Dermal Absorption of Elemental Impurities

Introduction

The skin is made up of several layers including stratum corneum[1], viable epidermis and dermis. The largest organ in the body this provides a formidable barrier. Within the skin overall the outer layer, the stratum corneum provides the most significant barrier and is rate limiting for any substance applied to the skin whether intentional in the form of an ointment deliberately applied or a contaminant inadvertently present on the skin. The stratum corneum is highly lipophilic with very low water content, as a result penetration of hydrophilic or charged molecules is particularly difficult, such species being unable to partition into the lipid layer.

Dermal Products – systemic exposure of impurities

A key factor in determination of toxic effects associated with topical application of drug products containing elemental impurities is the ability of the impurity to be absorbed through the skin and into the systemic circulation. A number of studies and reviews of metal absorption via topical exposure have been published in literature and have demonstrated that dermal absorption is generally less than oral absorption, which limits systemic exposure. For example, one study determined the dermal absorption of lead acetate from cosmetic preparations to be in the range of 0-0.3% (Moore et al., 1980) while oral absorption of lead from food and water is estimated at 50% and from soil is estimated at 30% (US EPA 2007).[2]

Thus it is important when determining a safe limit for topical exposure to elemental impurities from topical drug products to consider the information available from oral and parenteral routes, but not in isolation. If the toxic endpoint is due to systemic exposure, one can estimate systemic exposure from various routes (oral, dermal, etc.) as long as absorption and bioavailability from those routes are addressed.

Various *in silico*, *in vitro* and *in vivo* methods exist to estimate or measure dermal absorption of metals through skin. [3] Data from these studies of various metals is critical to understand systemic exposure for risk assessment purposes and to assure an adequate margin of safety for exposure to elemental impurities in topical drug products.

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[1]Topical and Transdermal Drug Delivery: What a Pharmacist Needs to Know

http://inetce.com/articles/pdf/221-146-04-054-H01.pdf

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Topical Exposure Calculation

Another important factor in understanding risks of exposure to impurities in topical products is that many of them have daily dosing which is not clearly defined in the product labeling. For example, a medicated shampoo will have simple instructions to wet hair, massage the product on head and rinse off. The amount to be used is thus determined by the personal preference of the consumer, not clearly defined by the manufacturer's usage instructions, thus making calculation of a daily dose an inexact science. That being the case, there are a number of published approaches used to estimate consumer exposure with habits and practices for various topical products. This exposure data is coupled with hazard data on the ingredients and impurities to conduct a quantitative risk assessment to help determine safe levels of the ingredients in these products.[4] Habits and practices data accounts for several variables in exposure, including the surface area of the skin that is exposed to the product, whether or not the products are rinsed off after brief exposure (and the residual amount left on the skin for possible absorption) or left on the skin after use, frequency of use and amount of product applied per use. This data can be used for deterministic or probabilistic exposure estimates.

The table below provides daily exposure calculations for many topical drug products using this established methodology when a clearly defined daily dose is not available.

[4]Api, A. M., Basketter, D. A., Cadby, P. A., Cano, M.-F., Ellis, G., Gerberick, G. F., Griem, P., McNamee, P. M., Ryan, C. A., Safford, R. Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Regulatory Toxicology and Pharmacology, **52** (2008) 3-23.

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Daily Exposure Calculations for Topical Drug Products

Product	Retention Factor*	g/application*	# of Application/day*	Estimated Daily Dose (application)	Surface Area (cm^2)*
Medicated Shampoo	0.01	11.8	2/day	236 mg/day	1440
Medicated Conditioner	0.01	14.1	2/day	282 mg/day	1440
Medicated Scalp Treatment (dandruff, hair loss, etc)	1.0	1^	2/day	2000 mg/day	1440
Facial Moisturizer Sunscreen	1.0	0.7	2.14/day	1500 mg/day	555
Facial Foundation Sunscreen	1.0	1.76	1/day	1760 mg/day	555
Body Sunscreen	1.0	7.8	2/day	15600 mg/day	17500
Lip Sunscreen or skin protectant	1.0	0.014	4/day	56 mg/day	4.8
Medicated Facial Treatment (i.e. leave-on acne treatment)	1.0	0.7	2.14/day	1500 mg/day	555
Medicated Facial Cleanser	0.01	0.8	2/day	1600 mg/day	555
Antibacterial Hand Soap	0.01	20 g/day[@]	10/day	200 mg/day	840
Hand Cream (skin protectant)	1.0	2.16 [@]	2/day	4320 mg/day	840
Antiperspirant – Spray	1.0	3.05	2/day	6100 mg/day[+]	200
Antiperspirant – Solid	1.0	1.35	2/day	1700 mg/day	200
Anti-Caries Toothpaste	0.1	1.35	2/day	270 mg/day	216.8
Anti- Plaque and Gingivitis Mouthwash	0.01	20[#]	2/day[#]	400 mg/day	216.8

* Api, AM, Basketter, DA, Cadby, PA, Cano, M-F, Ellis, G, Gerberick, GF, Griem, P, McNamee, PM, Ryan, CA, and Safford, R (2008). Dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients. *Regulatory Toxicology and Pharmacology* **52**:3-23 (unless otherwise noted)

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^ Label instructions for topical hair regrow th treatment

Proposed Rule – *Oral Health Care Drug Products for Over-the-Counter Human Use; Antigingivitis/Antiplaque Drug Products* Federal Register **68** (103) pg 32232-32287, 2003.

+ Total mass expelled from aerosol does not account for loss of propellant

Use of Quantitative Risk Assessment to Establish a Topical Limit

Below are case studies of exposure based risk assessments for lead in three different OTC topical drug products. This includes use of published data on dermal penetration of lead to derive a dermal PDE from the parenteral PDE. This dermal PDE for lead is then applied to exposure information from the table above to determine safe levels of lead as an impurity in the topical drug product type. These examples illustrate use of well accepted methodology to determine appropriate limits for lead in topical products. This type of approach can be reapplied for other impurities with the various OTC topical drug product exposures.

To provide guidance to the regulated industry for topical exposure to elemental impurities consideration should be given to reference this Quantitative Risk Assessment approach, with examples as below, within an appendix of ICH Q3D. This will give clarity on how to approach elemental impurities in topical products until such a time as specific limits can be set for topical exposure.

UV protection face cream, antiperspirant, anti-dandruff shampoo

Calculation (based on SCCS 2011) [5]**:**

The calculation of the SED will be as follows:

$$SED = \mathbf{A}\ (mg/kg\ bw/day) \times \mathbf{C}\ (\%)/100 \times \mathbf{DA_p}\ (\%)/100$$

SED (mg/kg bw/day) = Systemic Exposure Dosage
A (mg/kg bw/day) = Estimated daily exposure to a cosmetic product per kg body weight, based upon the amount applied and the frequency of application.
C (%) = Concentration of the ingredient under study in the finished cosmetic product on the application site.
DAp (%) = Dermal Absorption expressed as a percentage of the test dose assumed to be applied in real-life conditions.

Topical PDE for lead

- ICH Parenteral PDE for Pb = 5 µg/day (ICH Q3D Step 2b, 2013).
- Dermal penetration for Pb = 0.3% (Moore et al., 1980) [6].
- Topical PDE for Pb = Parenteral PDE/Dermal penetration = (5 µg Pb/day)/(0. 003) = 1.67 mg Pb/day.

[5] European Commission, Directorate-General for Health and Consumers, (2012) Scientific Committee on Consumer Safety (SCCS), "The SCCS's Notes of Guidance for the Testing of Cosmetic Substances and Their Safety Evaluation 8th Revision" 11 Dec 2012.

[6] Moore et al., 1980. The percutaneous absorption of lead-203 in humans from cosmetic preparations containing lead acetate as assessed by whole-body counting and other techniques. *Food Cosmetics Toxicology* **18**:399.

UV protection face cream (female)

Exposure

Daily exposure determined by habits and practices data (from US EPA Exposure Handbook and 90th percentile usage data from Colipa as reported in Api et al., 2008) [7].

- Retention factor = 1.0 (i.e., leave-on product)
- Product exposure = 1,500 mg/day or 2.70 mg/cm^2/day
- Default body weight = 60 kg
- Product exposure is 25 mg/kg/day = **A** in calculations
- Surface area of application = 555 cm^2
- Percutaneous absorption of lead = 0.3% (Moore et al., 1980)[5] which is **DA_p** after dividing by 100 in calculations.

Lead limits in a leave-on face cream OTC drug

SED = Systemic Exposure Dose = ICH Parenteral PDE for Pb = 5 µg/day (ICH Q3D Step 2b, 2013) divided by body weight (e.g., 60 kg for an adult female) = 83 x 10^{-6} mg/kg/day.

C = (% Pb concentration/100) in calculations that results in an equivalent parenteral Pb exposure to parenteral PDE.

C = SED/(A)(DA_p) = (83 x 10^{-6} mg/kg/day)/(25 mg/kg/day)(0.003) = 0.0011 or 0.11%.

Thus, a topical face cream with UV protectant can have up to 1,100 ppm Pb to equal the parenteral PDE limit for lead. This is explained by the limited dermal penetration rate of 0.3% versus 100% availability when administered parenterally.

Antiperspirant (solid)

Exposure

Daily exposure determined by habits and practices data (from US EPA Exposure Handbook and 90th percentile usage data from CTFA as reported in Api et al., 2008)[6].

- Retention factor = 1.0 (i.e., leave-on product)
- Product exposure = 1,700 mg/day or 8.5 mg/cm^2/day
- Default body weight = 60 kg
- Product exposure is 28 mg/kg/day = **A** in calculations
- Surface area of application = 100 cm^2/axilla

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[7] Api, AM, Basketter, DA, Cadby, PA, Cano, M-F, Ellis, G, Gerberick, GF, Griem, P, McNamee, PM, Ryan, CA, and Safford, R (2008). Dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients. *Regulatory Toxicology and Pharmacology* **52**:3-23.

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- Percutaneous absorption of lead = 0.3% (Moore et al., 1980)[5] which is **DA_p** after dividing by 100 in calculations.

Lead limits in an antiperspirant OTC drug

SED = Systemic Exposure Dose = ICH Parenteral PDE for Pb = 5 µg/day (ICH Q3D Step 2b, 2013) divided by body weight (e.g., 60 kg for an adult female) = 83 x 10^{-6} mg/kg/day.
C = (% Pb concentration/100) in calculations that results in an equivalent parenteral Pb exposure.
C = SED/(A)(DA_p) = (83 x 10^{-6} mg/kg/day)/(28 mg/kg/day)(0.003) = 0.00099 or 0.1%.
Thus, an antiperspirant solid can have up to 1,000 ppm Pb to equal the parenteral PDE limit for lead. This is explained by the limited dermal penetration rate of 0.3% versus 100% availability when administered parenterally.

Anti-dandruff shampoo

Exposure

Daily exposure determined by habits and practices data (from US EPA Exposure Handbook and 90th percentile usage data from CTFA as reported in Api et al., 2008)[6].

- Retention factor = 0.01 (i.e., rinse-off product applied to hair)
- Product application = 23,630 mg/day or 16.5 mg/cm^2/day applied
- Product exposure (application X retention factor) = 236.3 mg/day or 0.17 mg/cm^2/day
- Default body weight = 60 kg
- Product exposure is 3.94 mg/kg/day = **A** in calculations
- Surface area of application = 1,430 cm^2
- Percutaneous absorption of lead = 0.3% (Moore et al., 1980)[5] which is **DA_p** after dividing by 100 in calculations.

Lead limits in an anti-dandruff shampoo OTC drug

SED = Systemic Exposure Dose = ICH Parenteral PDE for Pb = 5 µg/day (ICH Q3D Step 2b, 2013) divided by body weight (e.g., 60 kg for an adult female) = 83 x 10^{-6} mg/kg/day.
C = (% Pb concentration/100) in calculations that results in an equivalent parenteral Pb exposure.
C = SED/(A)(DA_p) = (83 x 10^{-6} mg/kg/day)/(3.94 mg/kg/day)(0.003) = 0.0070 or 0.70%.
Thus, an anti-dandruff shampoo can have up to 7,000 ppm Pb to equal the parenteral PDE limit for lead. This is explained by the limited dermal penetration rate of 0.3% versus 100% availability when administered parenterally.

Conclusions:

The topical PDE for elemental impurities can be derived from the parenteral PDEs as long as systemic availability is accounted for with a dermal penetration correction. This can be applied to other routes of administration as well as long as systemic availability is accounted for via each route of administration.
As demonstrated above in the case studies, the concentration limit for lead in a topical OTC drug product is dependent upon the amount of product applied, the retention factor (i.e., residual amount of product left on skin for potential absorption), and the dermal penetration of the element of interest.

Elemental Impurity Data Reviews

This section briefly describes several reviews covering exposure to metals, primarily focused on environmental exposure from sources such as soils. While not an all inclusive and comprehensive review it does illustrate the fact that systemic absorption of metals through dermal exposure is generally low and is dependent upon multiple factors including size, charge and oxidation state of the metal. These include:

1. Hostynek et al. (1993) Metals and the skin. *Critical Reviews in Toxicology.* 23(2):171-235 [7].

This review seeks to provide a summary of the data relevant to the qualitative and where possible quantitative evaluation of metal permeation through skin. In total assessments are provided for some 31 elements, although coverage of class 1 metals is incomplete there being no assessment of mercury or lead. The overall conclusions of the paper are consistent with other assessments, concluding that dermal absorption of metals is a complex process affected by multiple factors including size, charge, oxidation state. The paper does not however draw any definitive overall conclusions regarding generic estimates of absorption, nor does it seek to generically compare rates to other routes of administration.

2. National Environmental Policy Institute[8] - Assessing the Bioavailability of Metals in Soil for Use in Human Health Risk Assessments. Bioavailability Policy Project Phase II Metals Task Force Report 2000.

   This review provides a thorough assessment of the available toxicological data for soil samples containing six metals, Arsenic, Cadmium, Chromium, Lead, Mercury and Nickel. This focuses on evaluations performed using soluble salt forms of the metals and assesses main routes of administration, including dermal limits. Conclusions relating to specific metals are described under the individual metal. The overriding conclusions are though that there is little data available to allow for the specific calculation of dermal exposure, however the data that are presented support the view that even when present in an aqueous soluble form, metals are poorly absorbed through the skin.

3. HERAG 1[9] - Health Risk Assessment Guidance For Metals - Assessment Of Occupational Dermal Exposure And Dermal Absorption For Metals And Inorganic Metal Compounds

This is a highly significant review that critically examines existing models used to estimate levels of dermal exposure and evaluates their value in assessing the absorption of inorganic metals. One of the most prevalent models used is the EASE[8] model, this defines default dermal absorption rates of 100 % or 10 % depending on the properties of the substance in question. Without relevant experimental data 10 % dermal absorption is used when the molecular weight (MW) of the substance is > 500 and the log P_{ow} is smaller than -1 or higher than 4, otherwise 100 % dermal absorption is used. The major issue with such an approach is that it was developed for organic chemical compounds, this approach is not considered relevant for metals, for the following reasons:

- log P_{ow} is a parameter which is not predictive of the properties of a metal or of an inorganic salt of a metal. Inorganic metal species do not permeate the skin by

[8] EASE – Estimation and Assessment of Substance Exposure, HSE 1999

passive diffusion. Instead, the uptake of metals largely depends on the presence of specific transport systems that provide biological gateways for the metal to cross the membrane.

- The dissolution of an inorganic metal compound or the metal itself on the skin surface will intrinsically require dissociation, and ultimately liberation of free metal cations. It is therefore obvious that the second criterion for assigning a dermal absorption rate (namely molecular weight) is irrelevant for metals, since under no circumstances is it feasible that any metal cation may exceed the cut-off value of "500".

The review repeatedly makes the point that such general approaches are not only scientifically flawed for the reasons described above, they grossly overestimate the actual levels of exposure.

Crucially the review cites recent studies that fundamentally challenge the ESE model, these data derived from studies performed on Zinc compounds (both soluble and insoluble forms). These show that penetration of the dermis by soluble zinc sulfate is low and that still lower penetration was observed for insoluble Zinc Oxide. The conclusion was that dissolution kinetics were the rate limiting factor. The results from these and other studies were summarized in the table opposite taken from the paper.

Table 21: Dermal absorption data for metals and inorganic metal compounds

Metal/compound	Test system	Results	References
Data as extracted and concluded upon in the various existing EU RA reports:			
Zinc oxide / Zinc sulphate	in vitro, porcine skin	2 % from liquid media 0.2 % from dust exposure (EU RAR assessment, Rapporteur: The Netherlands)	Grötsch (1999)
Cadmium metal, Cadmium oxide	(analogy)	< 1 % (EU RAR assessment, Rapporteur: Belgium)	EU RAR (2004)
Nickel metal, Nickel sulphate, Nickel chloride, Nickel nitrate, Nickel acetate	in vivo, human skin, tape stripping	0.2 % (EU RAR assessment, Rapporteur: Denmark)	Hostýnek et al. (2001a) Hostýnek et al. (2001b)
Nickel sulphate, Nickel chloride, Nickel nitrate, Nickel acetate	in vitro, human skin	2 % (EU RAR assessment, Rapporteur Denmark) 1 % when material bound to stratum corneum is discounted	Tanojo et al. (2001)
Diantimony trioxide	in vitro, human skin	0 - 0.1 %	Roper & Stupart (2006)
Copper compounds (not specified)	in vitro (unspecified)	0.3% soluble/insoluble Cu compounds (VRA Copper)	Roper (2003) Cage (2003)
Lead oxide	in vitro, human skin	0 - 0.1 % (VRA Lead)	Toner & Roper (2004)
Additional (non-exhaustive compilation) data made available from metal industries participating in HERAG:			
Zinc oxide	in vitro, porcine skin	< 0.1%	Gamer et al. (2006)
Aluminium chlorohydrate (^{26}Al-labelled)	in vivo, two human volunteers	0.012 % uptake (industry data)	Priest (2004), citing from Flarend et at. (2001)
Cobalt metal	in vitro (Franz diffusion cell, human skin)	Absorption not given as a percentage of the applied dose but as a steady-state flow of (0.0123 ± 0.0054) µg cm^{-2} h^{-1} with a lag time of (1.55 ± 0.71) h. Significant absorption only took place, when the metal was oxidised to Co^{2+} by stirring in artificial sweat for 30 minutes.	Filon et al. (2004)
Titanium dioxide	in vitro, porcine skin	< 0.1%	Gamer et al. (2006)

The paper made the following key conclusions based on these experimental data:

Recent studies conducted to OECD standards indicate dermal absorption rates to be at or below 0.3%.

There is no clear correlation between absorption and factors such as speciation, valency and /or water solubility.

Critically it concluded that it should be feasible to establish default absorption factors, it concluding that a default absorption rate of 1% was reasonable and adequately conservative.

Individual Metals

This section reviews some of the available information on relevant elemental impurities to illustrate that there is information available which can be useful in determining absorption capability of the metals through dermal exposure. It is not meant to be a comprehensive review of all available information.

Class 1 Metals

Arsenic

A white paper developed by the New Jersey Dept of Environmental protection, author Gloria Post Ph.D., D.A.B.T.

http://www.state.nj.us/dep/dsr/research/dermal-arsenic-whitepaper.pdf

Provides a useful summary of several studies pertaining to the dermal absorption of As. The data presented show that significant levels of As were found to penetrate the skin of mice, however this contrasted marketedly with the results obtained for human skin where levels were within the range 2-6% of the dose applied. The differences were attributed to the significant intra-species variation in skin thickness, that of a human being substantively greater.

The National Research Council (1999) evaluated the available information on this subject and stated that "these results indicate a low degree of systemic absorption of arsenic via the skin." ATSDR (2000) concluded that "it is usually considered that dermal uptake of arsenates and arsenites is sufficiently low that this route is unlikely to be of health concern …, but studies to test the validity of this assumption would be valuable." Arsenic does not act as a sensitizer upon casual skin contact due to poor skin-penetrating ability of its naturally occurring compounds.

Further studies were reported in Fundam Appl Toxicol. 1993 Apr;20(3):336-40. This study reported a low permeability coefficient of 2.71×10^{-6} following topical application of water containing radio-active As.

Cadmium

Absorption of cadmium through the skin is reported to be extremely low (0.5%)

Reference: http://corrosion-doctors.org/Elements-Toxic/Cadmium-absortion.htm

Other In vitro experiments were conducted using human skin, these involved exposure for 16 hours to 116 ppb $CdCl_2$ applied as 2.5 and 5 ul/cm2. Only 0.1 to 0.6% was found in the receptor solution.

The HREAG paper cites the RAR for Cadmium metal and Cadmium oxide, 2004 which concluded that percutaneous absorption is likely to be significantly less than 1%

Lead

Occupational Safety and Health Organisation (OSHA) concluded that Lead can be absorbed into your body by inhalation (breathing) and ingestion (eating). Lead (except for certain organic lead compounds not covered by the standard, such as tetraethyl lead) is not absorbed through your skin concluding that cutaneous [through the skin] absorption of lead

is limited (typically far less than 1%). The amount absorbed through the skin depends on the physical characteristics of the lead (ie, organic vs inorganic) and the integrity of the skin.

Moore, et al. in 1980 found dermal absorption of lead from topical preperations with lead acetate to be 0.3%.
The HERAG paper presented data from a study with a 1% lead oxide solution concluding that the dermal absorption rate was < 0.01%.

Ref:
Moore et al., 1980. The percutaneous absorption of lead-203 in humans from cosmetic preparations containing lead acetate as assessed by whole-body counting and other techniques. *Food Cosmetics Toxicology* **18**:399.

Mercury

Hostynek paper concludes that Mercury has the ability to penetrate the skin in all forms including the elemental form, outlining both intra and intercellular pathways. Data relating to studies performed using guinea pig skin and limited data relating to human skin are described. The data are complex showing an apparent non-linear dose response which was concluded to relate to significant skin retention, relating to reaction with skin proteins. There are no specific conclusions as to the actual level (%) absorbed.

Class 2 Metals

Reference Source: Hostynek et al. (1193) Metals and the skin. Critical Reviews in Toxicology. 23(2):171-235.

Vanadium

No specific studies were located regarding absorption in humans or animals after dermal exposure to vanadium, although absorption by this route is generally considered to be very low (WHO 1988). Absorption through the skin is thought to be quite minimal due to its low lipid/water solubility.

Molybdenum

Dermal reactions were observed following a single, semi-occlusive application of molybdenum disulphide to intact rabbit skin for four hours. Three rabbits were each administered a single dermal dose of 0.5 g of MoS_2 and observed for four days. The acute lethal dermal dose to rats of MoS_2> 2000 mg/kg bodyweight. Ten rats received a topical application of MoS_2 in 1% w/v aqueous methylcelulose, 2000mg/kg bodyweight. There was no systemic response to MoS2.

Cobalt

The human stratum corneum appears to be an effective barrier to penetration by cobalt. An attempt to measure the quantitative absorption of cobalt across human skin in vivo showed no detectable uptake over an 8-hour period.

Class 3

Copper

Results from two unpublished studies stated in HERAG paper to support a conservative dermal absorption factor of 0.3%.

Studies reported in Hostynek paper relate to organo-copper compounds and are no considered relevant.

Nickel

While the HERAG paper raises concerns over the methodology employed in the studies described, it reports that even in the highest example (one where data for level absorbed was combined with the level retained in the stratum corneum) the report absorption of a soluble salt form was reported to be only 2%.

Summary

There are many challenges presented when attempting to set limits for impurities in topically applied drug products. Elemental impurities are absorbed to different degrees through the skin barrier dependent upon oxidation state, size, charge, duration of exposure among many other factors. Additionally, many topically applied drug products do not have prescribed dosing amounts which requires any exposure assessment to estimate the amount of product to apply and the surface are of the skin which will be exposed to the product. Thus key factors in understanding the toxic effects of elemental impurities and building a safety assessment include the habits and practices of consumers using topically applied drug products to estimate appropriate exposure and the ability for the impurity to be absorbed through the skin and become available for systemic circulation. An approach with leverages this data can allow for the establishment of appropriate topical exposure limits for elemental impurities, either by ICH or by individual manufactuers, rather than simply applying oral or parenteral limits without consideration for relevant absorption and exposure factors associated with topical application.

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